REMARKS

Claims 1-80 are cancelled herewith without prejudice and the filing of the heretofore withdrawn claims in a divisional or continuing application in due course.

New claims 81-91 are submitted herewith and do not depart from the election already made by Applicant. All of the claims have been narrowed to require the analysis of the polypeptide under consideration in two or more reading frames, a limitation which did not appear in original claim 1. The "two reading frames" limitation now present in all of pending claims 81-91 did appear in original claim 80, which limitation was not the reason for the restriction of claim 80 on other grounds. The previously made species election of "mass" has been observed in that all the new claims submitted herewith are directed to assessing the predicted versus measured peptide mass signatures as recited in the claims. Attention has been made in drafting the new claims to accommodate the formal rejections and objections listed in the Office Action dated January 15, 2004. Support for the new claim language is found throughout the specification and, by large, the new dependent claims parallel the dependent claims previously under consideration. Entry of new claims 81-91 is respectfully requested.

Particularly in view of the "two reading frame" limitations of the newly submitted claims, it is believed that the asserted anticipation rejection of the claims over Little et al. and/or Garvin, both of record, will be seen to have been overcome. Garvin and Little et al. both teach a method for analyzing the nucleotide sequence of a polynucleotide by expressing a polypeptide from a single reading frame of a polynucleotide, purifying the polypeptide, measuing the mass of the polypeptide, and comparing the measured mass with the predicted mass of a presumably homolous "known polypeptide," in order to test the hypothesis that the test polynucleotide has the same sequence as the known polypeptide.

However, the present specification and claims recite the utility and means for expressing and analyzing polypeptides in two or more reading frames, and neither Little et al. nor Garvin teach or suggest any benefit of analyzing two reading frames simultaneously.

Indeed, the Little et al. specification teaches expressing a polypeptide from an alternative and non-natural reading frame of a polynucleotide, but there is neither a teaching nor a suggestion to express and to analyze two or more different polypeptides from two or more different reading frames of the same polynucleotide. Thus Little et al. teach (see column 14, lines 25 and 26) that the reading frame can be the natural reading frame or can be any other reading frame, and by referring only to a single reading frame at any time the possibility of two or more reading frames is not discussed or implied at all.

Likewise, Little et al. teach (column 15, lines 51-65):

> In one embodiment of the invention, the primers for the amplification are selected such that the amplification results in a nucleic acid which upon transcription and translation results in a non-naturally occurring polypeptide. In one embodiment, the polypeptide is encoded by an open reading frame which is not the open reading frame encoding the natural polypeptide. Accordingly, by appropriate primer design (in particular, by including an initiation codon downstream of a promoter in one of the primers), the polypeptide produced from the target nucleic acid is encoded by any of the two non-coding frames of the nucleic acid. This can be used to shift out of frame stop codons which prematurely truncate the protein and exclude relevant amino acids, or to make the polypeptide containing the amino acid repeat more soluble.

In the above quotation from Little et al., all of the relevant nouns and verbs are singular, not plural, making the references to single reading frames unequivocal.

Little et al. further teach (column 15, lines 66-67 and column 16, lines 1-11) that the non-naturally occurring polypeptide can also be encoded by a 5' or 3' non coding region of an exonic region of a nucleic acid, by an intron, or by a promoter sequence which

contains in one of the six frames (3 frames per strand) at least a portion of an open reading frame. In these situations, one primer for amplification of the target nucleic acid comprises a promoter and an initiation codon, such that the amplified nucleic acid can be in vitro transcribed and translated. Thus, Little et al. discuss the determination of the identity of a nucleotide sequence located in any region of a gene, so long as a polypeptide of at least 2, preferably 3, 4, or 5 amino acids is encoded by any one of the six frames. Once again, the Little et al. teaching unequivocally directs the practitioner to choose a single reading frame for analysis, not two or more reading frame for combined analysis, as is taught in the claimed invention.

Garvin does not add any disclosure to supplement Little et al. in any way as to teach or to suggest the two or more reading frame innovation. Thus the prior art does not even imply the benefit one can achieve by evaluating a polypeptide by expressing and analyzing two or more polypeptides encoded in two or more reading frames, as claimed. For a specification passage which highlights the practical importance of the two or more reading frames, the Examiner's attention is directed to paragraph 48 and the surrounding text.

Based on the foregoing amendments and remarks, entry and allowance of new claims 81-91 are respectfully requested.

Respectfully submitted,
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